Remarks/Arguments

Prior to the present amendment, Claims 44-47 and 49-51 were pending in this application. Applicants have canceled Claim 47and amended Claim 44 in order to expedite prosecution without acquiescence to any rejections and without prejudice to filing a continuation/divisional/continuation-in-part application directed to the canceled subject matter. Applicants believe that the current amendments place all claims in *prima facie* condition for allowance. Accordingly, the consideration and entry of the present amendment is respectfully requested.

I. Claim Rejections Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 44-47 and 49-51 stand rejected under 35 USC 112, first paragraph, for lack of enablement. Specifically, the Examiner asserts that allegedly "[t]he only use contemplated for the claimed invention is a therapeutic suppression of the immune system." Citing Kahan *et al.*, Piccotti *et al.*, and Campo *et al.*, the Examiner concludes that "while the art recognizes the MLR assay as accepted for screening for immunosuppressive molecules in vitro…this biological activity does not correlate to use of the claimed protein in a therapeutically effective manner, as the asserted use of the claimed invention proposes." (Page 3 of the instant Office action). For the reasons outlined below, Applicants respectfully disagree.

Applicants maintain the position that that Claims 44-47 and 49-51 satisfy the enablement requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in the Applicants' Responses dated March 2, 2004, May 19, 2005, October 30, 2006 and August 2, 2007, and Appeal Briefs dated March 3, 2006 and December 3, 2007.

The legal test of enablement was discussed previously, in Applicants' response of May 19, 2005, which is incorporated by reference herein. Applicants reiterate that the test of enablement is whether one reasonably skilled in the art could make or use the invention from disclosures in the patent application coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.,* 857F.2d 778, 785 (Fed. Cir. 1988), Emphasis added. Thus, in addition to the specific disclosure in the specification, general knowledge in the art at the time the invention was made also must be taken into account when assessing compliance with the enablement requirement of 35 U.S.C. §112, first paragraph. The M.P.E.P. further states, "The fact that experimentation may be complex does not necessarily

make it undue, if the art typically engages in such experimentation. *In re Certain Limited-charge cell Culture Microcarriers, 221 USPQ 1165, 1174* (Int'l Trade Comm'n 1983), *aff'. sub nom., Massachusetts Institute of Technology v A.B. Fortia,* 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) M.P.E.P. §2164.01. A considerable amount of experimentation is permissible, if it is merely routine.

Claims 44-47 and 49-51 are directed to the polypeptide of SEQ ID NO:290 (PRO335 polypeptide) where the polypeptide has a specific and useful function (*i.e.* as "immunostimulants" useful for boosting the immune system of an animal. Applicants submit that, the instant specification, at least in Example 74, page 208, line 27, and the disclosure of the Fong declaration (submitted with Applicants' response of October 25, 2004), describe the mixed lymphocyte reaction (MLR) assay, which the Examiner has acknowledged as sufficient to establish patentable utility under 35 U.S.C. §101 for the PRO335 polypeptide. The positive result for PRO335 in the MLR assay demonstrates that PRO335 is active as a stimulator of the proliferation of stimulated T-lymphocytes. Therefore, based on disclosures in the patent application coupled with information known in the art, one skilled in the art would know that agonistic immunostimulating polypeptides or antibodies are useful in treating, for instance, neoplastic tumors, or antagonistic antibodies –immunosuppressors, are useful for instance, in treating diseases like autoimmune or graft vs. host disease).

The MLR assay of the instant application is well-described in standard textbooks, including, for example, *Current Protocols in Immunology*, unit 3.12; edited by J.E. Coligan, A.M. Kruisbeek, D.H. Marglies, E.M. Shevach, W. Strober, National Institutes of Health, Published by John Wiley & Sons, Inc. (of record), which is referenced in Example 74.

In further support of utility based upon the MLR assay, Applicants have submitted (with their Response filed October 25, 2004) the Declaration of Sherman Fong, Ph.D. As Dr. Fong emphasizes, immunostimulants are important and highly desirable in the treatment of cancer and in enhancing the effectiveness of previously identified treatments for cancer. Costimulation of T cells can induce tumor regression and an antitumor response, both *in vitro* and *in vivo*. In paragraph 9 of his Declaration, Dr. Fong provides examples of important clinical applications for immune stimulants which have been shown to stimulate T-cell proliferation in the MLR assay. As Dr. Fong explains,

> IL-12 is a known immune stimulant, which has been shown to stimulate T-cell proliferation in the MLR assay. IL-12 was first identified in just such an MLR [Gubler et al. PNAS 88, 4143 (1991) (Exhibit C)]. In a recent cancer vaccine trial, researchers from the University of Chicago and Genetics Institute (Cambridge, MA) have demonstrated the efficacy of the approach, relying on the immune stimulatory activity of IL-12, for the treatment of melanoma. [Peterson et al. Journal of Clinical Oncology 21 (12). 2342-48 (2003) (Exhibit D)]
>
> Dr. Fong concludes that (paragraph 10):
>
> It is my considered scientific opinion that a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity at least 180% of the control, as specified in the present application, is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant."

Therefore, one skilled in the art would know that immunostimulating compounds like IL-12 or PRO335 of this invention, could be used in immunoadjuvant therapy (with tumor-specific antibodies) for the treatment of tumors (cancer) and could be administered alone or together with other agents to stimulate T cell proliferation/ activation (immune function). Accordingly, the positive results obtained in this assay clearly establish the immunostimulant utility for the PRO335 polypeptides claimed in the present application and its antibodies, and the specification, in turn, enables one skilled in the art to use the compounds for the asserted purpose.

Applicants further remind the Examiner that the instant invention is directed to a product, not a method of treatment, and the product is not required to have a specifically designated use such as for treating a particular disease, therefore, it should not be required that the claimed polypeptide has to be enabled for therapeutic uses in order to meet the requirement of 35 U.S.C. 112, first paragraph.

The Examiner alleges that "while the art recognizes the MLR assay as accepted for screening for immunosuppressive molecules in vitro...this biological activity does not correlate to use of the claimed protein in a therapeutically effective manner, as the asserted use of the claimed invention proposes." (Page 3 of the instant Office action).

Applicants respectfully disagree and submit that the MLR assay was routinely used in the art to identify immunostimulants or immunosuppressors, and additionally, were found to have *in vivo* utility, in the treatment of various diseases and conditions. Applicants incorporate by reference the articles and arguments presented in the Response filed October 30, 2006 (see

Santoli *et al.*, J. Immunol. 137:400-407 (1986); U.S. Patent Application No. 4,950,647, Reddy *et al.* (Infect. Immun. 44:339-343 (1984); Pahwa *et al.* (Proc. Natl. Acad. Sci. USA 86:5069-5073 (1989); Kirchner *et al.* (Br. J. Clin. Pharmacol. 46:5-10 (1998); Grabstein, K.H. *et al.*, Science 264:965-968 (1994); Chapoval *et al.* (J. Immunol. 161:6977-6984 (1998); Kasaian, M.T. *et al.*, Immunity 16:559-569 (2002); Ma *et al.* (J. Immunol. 171:608-615 (2003); Naito, K. *et al.*, J. Immunol. 142:1834-1839 (1989); Tarr, P.E, Med. Oncol. 13:133-140 (1996); Gennari *et al.* (Annals of Surgery, 220:68-76 (1994); Patterson, S. *et al.*, J. Immunol. 175:5087-5094 (2005); Toura *et al.* (J. Immunol. 163:2387-2391 (1999); Tsavaris *et al.*, Br. J. Cancer 87:21-27 (2002); Amirghofran, Z. *et al.*, Irn. J. Med. Sci. 25:119-124, (2000); Abolhassani, M., Brazilian Journal of Infectious Diseases 8:382-385, (2004); U.S. Patent No. 5,817,306, filed June 7, 1995; U.S. Patent No. 5,801,193, filed April 15, 1997; U.S. Patent No. 5,958,403, filed July 11, 1994 ; and U.S. Patent No. 5,648,376, filed January 19, 1995.

Applicants further note that a positive result as a stimulator in the MLR assay is also characteristic of molecules which have known *in vivo* utilities in the treatment of disorders for which stimulation of an immune response is desirable. For example, as discussed above IL-12 is a known immune stimulant, which has been shown to stimulate T-cell proliferation in the MLR assay (Gubler *et al.*, PNAS 88:4143 (1991) (submitted as Exhibit C in Applicants' Response filed October 25, 2004). In a recent cancer vaccine trial, researchers from the University of Chicago and Genetics Institute (Cambridge, MA) have demonstrated the efficacy of an approach relying on the immune stimulatory activity of IL-12 for the treatment of melanoma. Peterson *et al.*, J. Clin. Oncol. 21:2342-2348 (2003) (submitted as Exhibit D in Applicants' Response filed October 25, 2004).

Thus, the art as a whole, at the time of filing of the application, clearly establishes that the mixed lymphocyte reaction (MLR) is a widely used *in vitro* assay for identifying immunomostimulatory compounds and that the positive result as a stimulator in the MLR assay is widely accepted as a valid indication of therapeutic use in the treatment of disease conditions, including irradication of tumors. Applicants note that Dr. Fong's conclusions are consistent with what is accepted in the art. Accordingly, one skilled in the art would know how to use the compounds for the asserted purpose. Therefore, based on the art's teachings about the immunostimulatory activity of molecules, as a result of a positive MLR assay, would provide sufficient correlation to one skilled in the art, such that they would use the identified compounds

in the treatment of disorders for which stimulation of the immune system is beneficial, such as viral or bacterial infections, immune deficiencies, or tumor/cancer treatments.

The Examiner asserts that "the conclusions reached by Fung-Leung et al. are based on much more experimental data, assays and testing than that provided in the instant specification and the reference does not support the position that the MLR assay in the instant specification is predictive of use as a therapeutic compound for suppressing the immune response.." (Page 5-6 of the instant Office Action).

Applicants submit that Applicants need not disclose every teaching found in the post-filing references. Indeed, the present specification teaches enabling disclosure for the claimed invention and the post-filing references merely confirm the feasibility of the present invention as disclosed in the specification. The pre- and post filing published papers submitted by Applicants were intended to demonstrate the MLR assay was routinely used in the art to identify immunostimulants or immunosuppressors, and additionally, were found to have *in vivo* utility, in the treatment of various diseases and conditions. In addition to the specific disclosure in the specification, general knowledge in the art at the time the invention was made also must be taken into account when assessing compliance with the enablement requirement of 35 U.S.C. §112, first paragraph. Based on the art's teachings about the immunostimulatory activity of molecules, a result of a positive MLR assay would provide sufficient correlation to one skilled in the art, such that they would use the identified compounds in the treatment of disorders for which stimulation of the immune system is beneficial.

The Examiner asserts that Steinman and Thurner "address the utility of dendritic cells but not of a stimulatory MLR." (Page 6 of the instant Office Action).

Applicants submit that, as indicated in Unit 3.12.9 of Current Protocols in Immunology, dendritic cells are stimulator lymphocytes that induce responder T cells and activate them to increase cytokine production, cytokine receptor expression, and ultimately proliferation of the activated T cells, all of which are measurable in different assays. In the current MLR assay, suspensions of responder T cells were cultured with irradiated- or mitomycin treated- allogenic stimulator lymphocytes and thymidine uptake was measured to give a measure of T cell proliferation (see Current protocols, Unit 3.12.9). Current Protocols also teaches how stimulator lymphocytes (which includes dendritic cells) induce responder T cells and methods of preparing

them. Thus, based on this disclosure, one skilled in the art would know how to use dendritic cells in an MLR assay and how to measure T lymphocyte stimulation using thymidine uptake.

Regarding the rejection based on the Gubler reference, the Examiner alleges that it "describes the identification of IL-12 but uses MLR merely to compare activities, not as the basis for describing a molecule as a therapeutically useful immunostimulant." (Page 6 of the instant Office Action)

Applicants respectfully disagree. The use of the MLR assay has been extensively reviewed above under utility. Several peer-reviewed references and issued patents acknowledge its usefulness (see above, utility Section I). Applicants add that in fact, the Gubler reference clearly teaches the MLR assay (see the footnote of Table 1, Fig. 3(upper panel) and related discussions in the results section), where PHA-activated lymphoblasts prepared from human PBMCs were used to measure lymphoblast proliferation in a tritiated thymidine assay. This assay was a key assay in identifying IL-12 as an immunostimulant for T lymphocytes with immunoenhancing effects. Again, this is evidenced since Gubler discloses in column 1, page 4143 that "we initiated a search for novel cytokines that would synergize with suboptimal concentrations of recombinant IL-2 **to activate cytotoxic lymphocytes *in vitro*** and thus might have **synergistic immunoenhancing effects** when administered together with recombinant IL-2 *in vivo*" (emphasis added). Thus, the Gubler reference also supports the Applicants position that the MLR assay is very useful in identifying immunostimulants.

Regarding the rejection based on the Peterson reference and the use of IL-12 as an immunostimulant, the Examiner says that Peterson's subsequent research "was clearly required to suggest that the molecule could be used in this fashion". (Page 6 of the instant Office Action)

Again, Applicants respectfully disagree. Even though the Peterson's reference was published after the effective filing date of the instant application, it is an enabling reference, and its teachings are not contrary to the teachings of other references found in the art at, or before the time of filing of the instant application (July 11, 2001). For instance, Toura *et al.* (J. Immunol. 163:2387-2391 (1999); of record) disclosed that the "[i]njection of α-GalCer inhibits tumor metastasis almost completely in the liver or lung" (page 2387, col. 2). Toura *et al.* found that dendritic cells pulsed with α-GalCer are able to induce antitumor activity *in vivo* within 24 hours after cell transfer (page 2390, col. 2). Chapoval *et al.* (J. Immunol. 161:6977-6984 (1998); of

record) further studied the impact of IL-15 as an adjuvant to cancer therapy using cyclophosphamide (CY) in a mouse lung tumor model. GM-CSF is used in cancer immunotherapy to expand the population of dendritic cells before reinfusion into the patient (page 136, col. 2; Tarr, P.E, Med. Oncol. 13:133-140 (1996); of record). Kirchner *et al.* (Br. J. Clin. Pharmacol. 46:5-10 (1998); of record) stated that "[t]he use of recombinant human interleukin-2 (rhIL-2) has been recommended as the best current therapy for advanced renal cell carcinoma" (page 5, col. 1). Santoli *et al.*, J. Immunol. 137:400-407 (1986); of record), and in U.S. Patent Application No. 4,950,647 (column 9, lines 30-36; Table III; of record). Based upon its immunostimulatory activity, IL-2 has been demonstrated to have a range of utilities in the treatment of immune deficiencies, as well as in immunotherapy for cancer.

The Peterson reference further supports the use of the immunostimulant IL-12 in the treatment of a cancer, namely, melanoma. As exemplified form the list of references discussed above, the use of immunostimulants in the treatment of cancer was not concluded based on the Peterson studies alone. In fact, Gubler *et al.* (discussed in the Fong Declaration) also indicates on column 1, page 4143, that "we initiated a search for novel cytokines that would synergize with suboptimal concentrations of recombinant IL-2 **to activate cytotoxic lymphocytes *in vitro*** and thus might have **synergistic immunoenhancing effects** when administered together with recombinant IL-2 *in vivo*" (emphasis added). Therefore, Peterson *et al.* is in fact a supportive and enabling reference, indicating the use of immunostimulant molecules in the successful treatment of cancer.

The Examiner cites the reference Kahan (1991) for its statement that "no in vitro assay predicts or correlates with in vivo immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from in vitro systems to in vivo conditions," (page 3 of the instant Office action). The Examiner further cites Piccotti et al. (1999) to show that "IL-12 enhances alloantigen-specific immune function as determined by MLC, but this result in vitro does not result in a measurable response in vivo" (page 3 of the instant Office action). The Examiner further cites Campo et al. (2001) and says "while zinc suppresses alloreactivity in MLC, it does not decrease T-cell proliferation in vitro nor produce immunosupprepssive effects in vivo", (page 3 of the instant Office action).

Applicants respectfully disagree. Applicants submit that the Examiner has not correctly characterized the teachings of Kahan *et al.*, Picotti *et al.* and Campo *et al.* On the other hand,

these references, in combination with those cited by Applicants, demonstrate that, the art as a whole recognizes that the mixed lymphocyte reaction (MLR) is a widely used *in vitro* assay for identifying immunomodulatory compounds.

For instance, the statement by Kahan *et al.* (see above) is inconsistent with what was known and accepted in the art at the time of filing regarding the MLR assay. For example, U.S. Patent No. 5,817,306 states, "The mixed lymphocyte response (MLR) and phytohemagglutinin A (PHA) assays are valuable for identifying immune suppressive molecules *in vitro* that are useful for treating graft versus host disease. **The results obtained from these assays are generally predictive of their *in vivo* effectiveness**." (Column 12, lines 36-41; emphasis added). U.S. Patent No. 5,801,193, filed April 15, 1997, states that "[t]he **MLR is an assay recognized by those skilled in the art as an in vitro predictor of in vivo immunosuppressant activity**." (Column 8, lines 8-10, emphasis added). U.S. Patent No. 5,648,376, filed January 19, 1995, states that "[a] measure of immunosuppression that serves as a model for transplantation rejection is inhibition of cell proliferation in a mixed lymphocyte reaction (MLR) assay." (Column 11, lines 24-26). Therefore, Kahan's quoted statement contradicts well established scientific wisdom. As discussed extensively above, in fact, the MLR assay has been extensively used and is the best *in vitro* model for screening immunostimulatory agents. In fact, the examiner's cited reference, Picotti *et al.*, also supports this point, since the authors extensively used the MLC assay in their studies.

Picotti *et al.* studied the mechanism of alloimmune response and graft rejections. Picotti *et al.* in fact, confirms that "IL-12 is a key cytokine involved in promoting cell mediated immune responses in vivo" (page 1459, col. 1). Picotti *et al.* also showed that the IL-12R gamma subunit was critical for IL-12 driven enhanced alloimmune response ***in vitro* and *in vivo*** (see abstract). Based on their studies, one skilled in the art would know that immunostimulating compounds like IL-12 (or of this invention) could be used in immunoadjuvant therapy (with tumor-specific antibodies, which is also discussed in the Fong Declaration, Petersen *et al.* reference)for the treatment of tumors (cancer). One skilled in the art would know that immunostimulant molecules can be administered alone or together with other agents to stimulate T cell proliferation/ activation (immune function) ad therefore, one skilled in the art would know that such agents can be used to stimulate an antitumor response to a tumor antigen. If anything, Picotti *et al.*, supports the point that immunostimulants are useful for treating tumors.

Applicants respectfully point out that the Examiner has misinterpreted this statement, due to the fact that the authors refer to two different types of immunosuppressive effects. Campo *et al.* set out to look for an inhibitor of MHC *in vitro* which would have the fewest side effects *in vivo* (see Abstract). The authors note that high concentrations of zinc "impair **all** T cell and monocyte function" (page 20; emphasis added). The authors took this impairment as an indicator of toxicity, and therefore intentionally used concentrations of zinc below that at which all T-cell function was impaired, in order to identify a concentration range that would not result in toxic effects. However, that does not mean that Campo *et al.* found zinc to have no immunosuppressive activity *in vivo*. In fact, the authors conclude, based upon their MLC results, that "zinc **could become an immunosuppressant in transplantation medicine** without toxic side effects" (page 21; emphasis added). Thus Campo *et al.* supports Applicants' position that those of skill in the art would interpret the results of MLC assays as having physiological relevance.

Applicants note that the Examiner has failed to point out several instances within these cited references wherein the authors stated that the MLR is an important method with a good predictive value. For example, Campo *et al.* teach that "the human mixed lymphocyte culture (MLC) is an important method to test donor-recipient compatibility in bone marrow transplantation. It could be shown that cytokine release, especially IFN-gamma, **has a very good predictive value with regard to the transplantation outcome**, as cytokines play a major role in the generation of an alloreactive immune response and for the induction of graft rejection ***in vivo***.....Landolfo *et al.* inhibited T-cell reactivity by the addition of anti-IFN-gamma **both *in vitro* and *in vivo***" (see page 18; emphasis added). Finally, Campo *et al.* teaches that "cyclosporin A, FK506, and other substances are used to prevent graft rejection. **In vitro experiments revealed an inhibition of the MLC**" (page 16). Thus the teachings of Campo *et al.* confirm that inhibition of the MLR is observed for known immunoinhibitory molecules, that are in actual clinical use.

Thus, while there are instances of unpredictability in some studies using the MLR assay, there are many more studies showing the usefulness and predictable results using MLR, as exemplified by the studies by Picotti, Landolfo and the IFN-gamma study and all the references submitted by the Applicants in this response. Therefore, the teachings within Kahan *et al.*, Piccotti *et al.*, Campo *et al.*, in fact, support the usefulness of the MLR assay.

The Examiner further asserts that "the results of the MLR assay in the instant specification are merely preliminary, and much more experimentation is necessary for one of ordinary skill in the art to use the claimed invention in the manner disclosed." (Page 6 of the instant Office Action)

Applicants respectfully submit that enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive." As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." The M.P.E.P. further explains that "If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied." Applicants note that the specification clearly indicates that the claimed polypeptides are useful in the treatment of undesirable immune responses. The use of immunosuppressive molecules in the treatment of such disorders is well known in the art, as indicated by Kahan *et al.*, Picotti *et al.* and Campo *et al.*, made of record by the Examiner, as well as the references and U.S. Patents, previously discussed and made of record by Applicants. Thus any further experimentation required for determining, for example, a particular dosage or method for the administration of PRO335 would not be considered undue.

Further, with respect to disclosure of the results of *in vitro* assays, the M.P.E.P. states that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995)."

The M.P.E.P. also makes it clear that the burden of proof is on the Examiner, to demonstrate lack of correlation for an *in vitro* model. "(s)ince the initial burden is on the

examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example." A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka,* wherein the court stated that "based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence."

As discussed above, MLR was routinely used in the art to identify immunostimulants or immunosuppressors, and additionally, were found to have *in vivo* utility, in the treatment of various diseases and conditions. Further, the importance of immunostimulants in the treatment of cancer or in enhancing the effectiveness of previously identified treatments for cancer, including tumor-specific antibodies were well known in the art at the time of filing of the instant application, as discussed in several references cited above. For instance, costimulation of T cells inducing tumor regression and an antitumor response, both *in vitro* and *in vivo* was known (for e.g., Steinman *et al.* -submitted as Exhibit B with the Response filed October 25, 2004). Thus, one skilled in the art would know that immunostimulating compounds like IL-12 or PRO335 of this invention, could be useful in immunoadjuvant therapies, for the treatment of tumors (cancer) and could be administered either alone or together with other agents to stimulate T cell proliferation/ activation (immune function). These could be done without undue experimentation.

The Examiner asserts that "Current Protocols in Immunology in fact describes many variables that must be controlled for. In the instant application, no such controls, such as for maximum response or for the inherent variability of individual responses, are provided. There is no indication of statistical significance of the results. There are no autologous controls. No correlation is provided to any particular in vivo function; there is no guidance to indicate that PRO335 could be used to any therapeutic effect for the treatment of diseases such as cancer or HIV." (Page 6 of the instant Office Action)

Applicants respectfully maintain their position, as presented in the Response filed October 30, 2006, that the controls cited by the Examiner were only needed for the purpose of evaluating the properties of the stimulator cells. Such determinations, however, are not required for the MLR assay of Example 74, and thus these controls are not "essential". Because the response in the test reaction is compared to a negative control reaction, and because both reactions use the same stimulator and responder cells at the same time, additional controls to determine the precise properties of these cells are not required. Further, the protocols described in the instant specification are consistent with those accepted in the art. For example, U.S. Patent No. 4,950,647, which demonstrated the immunoenhancing activity of the compound 6-Amino(2-deoxy-alpha-D-erythro-petofuranosyl)imidazo[4,5,-C] pyridine-4-one using the MLR assay, did not disclose the use of any additional controls beyond those disclosed in the instant application.

With respect to the statistical significance of the results, Applicants respectfully submit that these remarks are a clear indication that the Examiner applies a heightened legal standard that is inappropriate for determining if the "enablement" standard of the Patent Statute is met. First of all, as evidenced in the numerous references made of record by Applicants, knowledge in the art at the time the invention was filed clearly demonstrate an ability to determine statistical significance of results generated from the MLR assay. Further, the MLR assay described herein is a comparative one (increases of greater than or equal to 180% is preferred), meaning that the utility is based upon a comparison of relative expression levels between a known polypeptide and an unknown PRO molecule. Useful information is obtained when a relative differences are observed, and this is routine in biological testing. Applicants expressly assert that the observed difference for PRO335 is significant (this point is further discussed below based on U.S. Patent No. 4,950,647). For instance, Example 74 of the specification makes clear the standard to be used to determine whether a positive result in the MLR assay is significant, stating that "[p]ositive increases over control in this assay are considered to be positive results, with increases of greater than or equal to 180% being preferred and that PRO335 tested positive in this assay. However, any value greater than control indicates a stimulatory effect for the test protein" (page 203, line 27). Therefore, this disclosure clearly meets the standard for statistical significance. The Examiner seems to focus on exactly how much higher (*i.e.*, requiring Applicants to provide "relative or absolute levels" and statistical analyses), but Applicants

submit that this is not relevant to the issue at hand, nor is it required for the claimed invention to be useful.

Applicants further submit that the term "positive increases over control" would readily be understood by one skilled in the art. For instance, the Examiner's attention is directed to U.S. Patent No. 4,950,647 (of record), which claims immunoenhancing compositions comprising the compound 6-Amino(2-deoxy-alpha-D-erythro-petofuranosyl)imidazo[4,5,-C] pyridine-4-one. The immunoenhancing activity of the claimed compound was determined in part by the use of the MLR assay, as shown in Example IV (column 13, lines 20-37). The claimed compound increased the response in the MLR, with a maximum increase of 191% as compared to control, as shown in Table VII. IL-2 showed a similar level of stimulation of the MLR (with a maximum of 200% as compared to control) as shown in Table III. Thus this patent supports the threshold of 180% described in the instant specification as showing significant stimulatory activity. Given that 6-Amino(2-deoxy-alpha-D-erythro-petofuranosyl)imidazo[4,5,-C] pyridine-4-one was identified as an immunostimulatory compound based upon a reported increase in the MLR assay of 191% as compared to control, the activity for PRO335 of greater than or equal to 180% as compared to control clearly meets the standard accepted in the art as demonstrating patentable utility.

Therefore, this rejection requiring allegedly essential controls and statistical data are not appropriate, as relevant even from the art, and should be withdrawn.

As set forth in M.P.E.P, 2107 II(B)(I), if the applicant has asserted that the claimed invention is useful for any particular practical purpose, and the assertion would be considered credible by a person of ordinary skill in the art, a rejection based on lack of utility should not be imposed. The logic underlying the asserted utilities in the present case is not inconsistent with general knowledge in the art, and would be considered credible by a person skilled in the art. It is, of course, always possible that an invention fails on its way of development to a commercial product. Thus, despite recent advances in rational drug design, a large percentage of drug candidates fails, and never makes it into a drug product. However, the USPTO is not the FDA, the law does not require that a product (drug or diagnostic) be currently available to the public in order to satisfy the utility requirement.

Further, the test of enablement is whether one reasonably skilled in the art could make or use the invention from disclosures in the patent application coupled with information known in

the art without undue experimentation. *United States v. Telectronics, Inc.,* 857F.2d 778, 785 (Fed. Cir. 1988), Emphasis added. Thus, in addition to the specific disclosure in the specification, general knowledge in the art at the time the invention was made also must be taken into account when assessing compliance with the enablement requirement of 35 U.S.C. §112, first paragraph. The full-length PRO335 polypeptide having the amino acid sequence of SEQ ID NO:290 is described in the instant specification at, for example, page 50-51, lines 1-22, in Figure 102 and in SEQ ID NO:290. Support for the preparation and uses of antibodies is found throughout the specification, including, for example, Example 57-59, pages 199-200.

Applicants respectfully remind the Examiner that the skilled artisan in the field of Immunology and Immunotherapeutics, at the effective filing date of September 17, 1998, would likely be a person with a Ph. D. or M.D. degree, sometimes both, with extensive experience. As such, one skilled in the art could easily test whether the claimed PRO335 polypeptide can elicit T-cell stimulatory activity using the MLR assay (as described in the Example 74 of the specification and in Current Protocols). As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." M.P.E.P. §2164.01 Thus, one would have known how to make and use the present invention at the effective date of the application.

In summary, in view of the foregoing arguments, the examples and specific teachings provided in the specification and general knowledge in the art, one skilled in the art at the priority date of the present application would have clearly known how to use the invention within the full scope of the claims pending. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

II. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 44, 47, 50 and 51 remain rejected under 35 U.S.C. §112, first paragraph, allegedly "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s),....had possession of the claimed invention." (Page 8 of the instant Office Action). Specifically, the Examiner asserts that "[w]hile one of skill in the art can readily envision numerable species of polypeptide sequences that are at least a given % identity to a reference polypeptide, one cannot envision

which of these polypeptides would comprise the "extracellular domain" of the polypeptide of SEQ ID NO:290.

In order to expedite prosecution, Applicants have cancelled Claim 47 and amended Claim 44 to remove references to the extracelluar domain of PRO335 without acquiescence to any rejections and without prejudice to filing a continuation application directed to the canceled subject matter.

Cancellation of Claim 47and amendment of Claim 44 renders this rejection moot. Therefore, withdrawal of the written description rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

CONCLUSION

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any additional fees for extension of time, or credit overpayment to Deposit Account No. 50-4634 (Attorney Docket No.: **123851-181890 (GNE-1618P2C46)**. Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: May 14, 2009

By: _____
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